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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/051,159	01/13/99	BALMAIN	A	CCI-005US

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EXAMINER	
BRUNOVSKIS,P	
ART UNIT	**PAPER NUMBER**
1632	19

DATE MAILED: 11/07/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/051,159	BALMAIN ET AL.	
	Examiner	Art Unit	
	Peter Brunovskis	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response filed 8/20/01 (Paper No. 18) has been entered. Amendments of claims 1-19, 21, 23, and 24 is acknowledged.

Any objections or rejections made in a previous Office Action that are not herein reinstated have been withdrawn. Unless otherwise indicated, arguments directed to rejections rendered moot by Applicants amendments or Examiner's withdrawal will not be further addressed or acknowledged. Claims 1-24 are pending in the instant application.

Oath/Declaration

Entry of Applicant's declaration is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is indefinite because it is unclear how the claim further limits or is patentably distinct from its base claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, and 20-24 are rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office Action of 2/15/01 and for the reasons set forth below as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification provides a limited description of promoters that meet the limitations of the instant claims; importantly, the only promoters adequately described in the instant specification are those whose function is *suppressed in non-tumor cells, but up-regulated in tumor cells in accordance with a particular p53 or p16 status*. For example, the specification only describes a limited number of promoters appropriate for a "Type I genetic unit", positively responsive to cells carrying a mutant p53 or null 53 phenotype and negatively responsive to normal wtp53-positive cells (e.g. HSP70, MDR1, PCNA, p. 10; and certain modified HSP70 promoters variants carrying inserted lacO-, tetO- or Gal-4 binding sites, e.g. pp. 35-37). The only

other candidate "Type I" promoter for use with the claimed method not directly linked to the mutant p53 "gain of function" pathway is the p16 INK4A promoter.

Applicant's arguments filed 8/20/01 have been fully considered but they are not persuasive. The response contends that "[w]ritten description may be satisfied through disclosure of relevant identifying characteristics, i.e. structure, other physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination or such characteristics" (paragr. abridg. P. 10-11). The response further contends that the claimed genus of promoters is adequately defined by structural features that are described in the specification, recited in the claims, and commonly possessed by its members and that the specification teaches that the promoters possess certain functional characteristics. The problem with the instant claims is that are solely defined by functional characteristics that are ***not*** coupled with a known or disclosd correlation between function and structure in accordance with the Interim Guidelines for the Written Description Requirement.

The specification fails to provide any core structure linking members of the claimed genus of promoters. As previously noted in the Office Action of 8/20/01, possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The specification does not set forth

any relevant identifying characteristics that would allow a skilled artisan to recognize whether a given promoter met the functional limitations set forth in the instant claims. For example, the specification does not what common structural features in the HSP70, MDR1, PCNA, or p16 INK4A promoters account for their meeting the requirements of a Type I promoter. Having to test a promoter to determine whether it has the required characteristics is *prima facie* evidence for lack of possession for the broadly claimed genus of embodiments at the time of filing. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). Amending the claims to recite *specific* embodiments comprising, e.g. specific p53 pathway promoters having a known or disclosed correlation between function and structure would obviate the rejection.

Claims 1-24 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office Action of 2/15/01 and for the reasons set forth below, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The disclosure is largely limited to compositions comprising use of a first promoter down-regulated in non-tumour cells through the action of wild-type p53, but up-regulated in

tumor cells by mutant p53, wherein a second wild-type p53-responsive promoter operatively linked to an effector product is included to down-regulate "leaky expression" from the first promoter in non-tumour cells. Apart from those embodiments specifically disclosed in the specification for use in up-regulating antitumour agents in tumor cells, while down-regulating those same agents in normal cells through a p53 pathway (i.e. using either HSP70-, MDR1-, PCNA promoters or variants thereof; or possibly p16INKK4A pathway), the specification fails to provide sufficient guidance teaching how to make or use any other compositions for use in a non-p53 based method or in accordance with the composition of claim 1, wherein the first promoter is suppressed in non-tumor cells relative to tumor cells and wherein the second gene suppressing said first promoter is up-regulated in non-tumor cells relative to tumor so to selectively efffect expression of the first gene in tumor cells only. Moreover, the selective expression characteristics are only observed in particular types of tumor cells exhibiting, e.g. a particular mutant p53 "gain of function" phenotype.

In spite of the assertion in the specification that "the general concept of the invention may be applicable using other genes to up-regulate the antitumour agent in tumour cells and to down-regulate it in normal cells" (top paragraph, p. 6), the specification fails in its burden to provide sufficient guidance on how to identify other such genes or promoters commensurate with the scope with the claimed invention. Extrapolation of this "concept" to other as yet undeveloped promoters or other as yet undiscovered genes or promoters in accordance with the claimed invention falls under the "germ of an idea" concept defined by the CAFC. The court has stated

that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). The claimed methods of transfer constitute such a "germ of an idea". Although the specification provides novel aspects as related to a p53-centered system, it fails to provide the other requisite novel aspects to enable, absent undue experimentation, other compositions or methods in accordance with the *scope* of the claimed subject matter.

Applicant's arguments filed 8/20/01 have been fully considered but they are not persuasive. The response contends that "the specification provides both working examples and ample guidance for testing any promoter or gene to determine whether it functions within the scope of the claimed invention" (response, p. 12). Without specific guidance concerning the nature of which promoters to test or how to identify such, it would require undue experimentation to test the vast universe of promoters to identify other members falling within the broadly claimed genus. The response asserts characterizes the "experimentation...required to make or use promoters or genes within the scope of the present claims as routine, not undue, experimentation". However, the response fails to provide any substantive evidence to support this assertion or any evidence that identification of such promoters was routinely performed at the time of filing.

Cell claims 20 and 21 and method claims 22-23 embrace embodiments that read on in vivo gene therapy which is not enabled by the instant application. The response alleges that claims 20-23 were rejected for lack of utility (p. 13). This is not an accurate statement of the record. When read in light of the specification, the only substantial or well-established utility that can be gleaned from the claimed compositions or methods of claims 20-23 is gene therapy for cancer. Absent evidence of any other non-therapeutic utility, for purposes of enablement, claims 20-23 were evaluated to the extent that the specification provides an enabling disclosure for in vivo gene therapy.

In response to the prima facie evidence for lack of enablement of these claims, Applicants set forth various submitted articles discussing the state of gene therapy and that allegedly support the viability of gene therapy as a therapeutic approach. Rather than directly address the specific prima facie evidence for lack of enablement as directed to the claims which read on gene therapy, the response instead selectively recites isolated passages discussing the optimism about success in gene therapy (see e.g. Crystal on p. 14 and Miller on p. 15). Despite such optimism, the fact remains that at the time of filing, successful practice of gene therapy was not routinely obtained. None of the evidence submitted by Applicants indicates that cancer gene therapy was routinely performed at the time of filing. Absent evidence of reduction to practice in the specification or declaratory post-filing evidence of such using the methods and guidance disclosed in the instant application, there is no expectation of success for the claimed subject matter as it relates to gene therapy. Applicants have failed to provide sufficient evidence to support their assertion (p. 16)

that "it would require undue experimentation by one of ordinary skill in the art to determine appropriate regimens...for practicing the claimed *in vivo* methods". This is particularly true given the lack of success in the art at the time of filing. Given this well-documented lack of success, the fact that many clinical trials for gene therapy have been performed and that many companies are *developing* approaches for such can only be interpreted to indicate that more work needs to be done to enable the practice of gene therapy.

To enable the instantly claimed embodiments directed to gene therapy, the specification must provide the critical mass of novel aspects of the invention for the successful practice of gene therapy. Although the p53-pathway-directed vector compositions of the instant application provides one sub-embodiment that would be useful in principle for ***developing*** a gene therapy against certain types of cancers, the novel features for enabling such cancer gene therapy must ***additionally*** address e.g. the problems and unpredictability in the art as directed to targeting and achievement of efficacious transgene levels in vivo comprising sufficiently novel aspects in a methodological sense to overcome the problems in the art. Absent sufficient *specific* guidance for the novel aspects which enable *in vivo* targeting, delivery, and selective tumor-specific expression of e.g. cytotoxins provide a therapeutic benefit, such that the approach overcomes the problems and lack of success in the art at the time of filing, it would require undue experimentation to enable the scope of the claimed compositions and methods recited in claims 20-23. Amending the claims to be directed at isolated cells or in vitro methods would obviate

this particular basis for the rejection (in addition to reciting specific enabled embodiments in said claims).

No claims are allowed.

The claims appear to be free of the art. Amendment of the claims to recite specific p53/p16INK4A-pathway directed embodiments and/or isolated cells or *in vitro* methods obviating the 35 U.S.C. 112, first paragraph rejections above would appear to render the claims in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Patent Analyst, Patsy Zimmerman whose telephone number is (703) 308-8338.

Deborah Crouch

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632

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